BILIARY ATRESIA

Incidence.

Biliary atresia has been detected in 1/10,000-15,000 live births, idiopathic neonatal hepatitis in 1/5,000-10,000. Intrahepatic bile duct paucity appears much less commonly, in about 1/50,000-75,000 live births.

Differentiation of Idiopathic Neonatal Hepatitis from Biliary Atresia.

It may be difficult to clearly differentiate infants with biliary atresia, who require surgical correction, from those with intrahepatic disease (neonatal hepatitis) and patent bile ducts. No single biochemical test or imaging procedure is entirely satisfactory. Diagnostic schemas incorporate clinical, historical, biochemical, and radiologic features.

Idiopathic neonatal hepatitis has a familial incidence of approximately 20%, whereas biliary atresia is unlikely to recur within the same family. A few infants with biliary atresia have an increased incidence of other abnormalities, such as the polysplenia syndrome with abdominal heterotaxia, malrotation, levocardia, and intra-abdominal vascular anomalies. Neonatal hepatitis appears to be more common in premature or small for gestational age infants. Persistently acholic stools suggest biliary obstruction (biliary atresia), but patients with severe idiopathic neonatal hepatitis may have a transient severe impairment of bile excretion. Consistently pigmented stools rule against biliary atresia. The finding of bile-stained fluid on duodenal intubation also excludes biliary atresia. Palpation of the liver may find an abnormal size or consistency in patients with extrahepatic biliary atresia; this is less common with neonatal hepatitis.

Abdominal ultrasound is a helpful diagnostic tool in the evaluation of neonatal cholestasis because it will identify choledocholithiasis, perforation of the bile duct, or other structural abnormalities of the biliary tree such as a choledochal cyst. In patients with biliary atresia, ultrasound may detect associated anomalies such as abdominal polysplenia and vascular malformations. The gallbladder is either not visualized or a micro-gallbladder is seen in patients with biliary atresia. Children with intrahepatic cholestasis caused by idiopathic neonatal hepatitis, cystic fibrosis, or total parenteral nutrition may have similar ultrasonographic findings. Ultrasonographic *triangular cord (TC) sign*, which represents a cone-shaped fibrotic mass cranial to the bifurcation of the portal vein, may be seen in patients with biliary atresia. The echogenic density, which represents the fibrous remnants at the porta hepatis of biliary atresia cases at surgery, may be a helpful diagnostic tool in the evaluation of patients with neonatal cholestasis.

338.1 Inherited Deficient Conjugation of Bilirubin (Familial Nonhemolytic Unconjugated Hyperbilirubinemia)

Hepatic glucuronyl transferase activity (Chapter 91.3) is deficient in two genetically and functionally distinct disorders (Crigler-Najjar syndromes, type I and II), producing congenital nonobstructive, nonhemolytic, unconjugated hyperbilirubinemia. The molecular mechanism of the various Crigler-Najjar syndromes is complex. This is partly because the activity of multiple glucuronyl transferase isoforms is deficient in various phenotypes of the Crigler-Najjar syndrome. Low enzyme levels with unconjugated hyperbilirubinemia also occur in **Gilbert syndrome**, a benign disorder, commonly caused by a polymorphism in the promoter region of the transferase gene.

Crigler-Najjar Syndrome (Type I Glucuronyl Transferase Deficiency).

This form is inherited as an autosomal recessive trait and is due to mutations in the UDP(B)-GT gene. Parents of affected children have partial defects in conjugation as determined by hepatic enzyme assay or by measurement of glucuronide formation, but their serum bilirubin concentrations are normal.

CLINICAL MANIFESTATIONS.

Severe unconjugated hyperbilirubinemia develops in homozygous infants during the first 3 days of life, and without treatment, serum concentrations of 25-35 mg/dL are reached during the 1st mo. Kernicterus, an almost universal complication of this disorder, is usually first noted in the early neonatal period, but some treated infants have survived childhood without clinical sequelae. Stools are pale yellow. Persistence of unconjugated hyperbilirubinema at levels above 20 mg/dL after the 1st wk of life in the absence of hemolysis should suggest the syndrome.

DIAGNOSIS.

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The diagnosis of Crigler-Najjar syndrome is based on the early age of onset and the extreme level of bilirubin elevation in the absence of hemolysis. In the bile, bilirubin concentration is less than 10 mg/dL compared with normal concentrations of 50-100 mg/dL, and there is no bilirubin glucuronide. Definitive diagnosis is established by measuring hepatic glucuronyl transferase activity in a liver specimen obtained by a closed biopsy; open biopsy should be avoided because surgery and anesthesia may precipitate kernicterus. DNA diagnosis is also available. Identification of the heterozygous state in the parents is also strongly suggestive of the diagnosis. Differential diagnosis is discussed in Chapter 91.3. Type II disease may be distinguished from type I by the marked decline in serum bilirubin level that occurs in type II disease after 1 wk of treatment with phenobarbital.

TREATMENT.

Serum bilirubin concentration should be kept below 20 mg/dL for at least the first 2-4 wk of life; in low birthweight infants, the levels should be kept lower. This usually requires repeated exchange transfusions and phototherapy. Phenobarbital therapy should be considered to determine responsiveness and differentiation between type I and II. Because the risk of kernicterus persists into adult life, although the serum bilirubin levels required to produce brain injury beyond the neonatal period are considerably higher (usually >35 mg/dL), phototherapy is generally continued throughout the early years of life. In older infants and children, phototherapy is used mainly during sleep in order not to interfere with normal activities. However, despite the administration of increasing intensities of light for longer periods, the serum bilirubin decrement response to phototherapy decreases with age. Adjuvant therapy using agents that bind photobilirubin products such as calcium phosphate, cholestyramine, or agar may be used to interfere with the enterohepatic recirculation of bilirubin. Prompt treatment of intercurrent infections, febrile episodes, and other types of illness may help prevent the later development of kernicterus, which may occur at bilirubin levels of 45-55 mg/dL. All patients with type I have eventually experienced severe kernicterus by young adulthood, despite vigorous continuous management that maintained neurologic normality during childhood. Orthotopic hepatic transplantation cures the disease and has been successful in a small number of patients, and isolated hepatocyte transplantation has been reported in one patient. Other therapeutic modalities have included plasmapheresis and limitation of bilirubin production. The latter option, inhibiting bilirubin generation, is possible via inhibition of heme oxygenase using metalloporphyrin therapy. Genetically engineered enzymatic replacement therapy and liver-directed gene therapy remain potential therapeutic options in the future.

Crigler-Najjar Syndrome (Type II Glucuronyl Transferase Deficiency).

This autosomal dominant disease with marked variability of penetrance may present in a manner similar to type I syndrome, or it may be a less severe disorder, occasionally even without neonatal manifestations. Crigler-Najjar syndrome type II is caused by homozygous missense mutation in glucuronyl transferase isoform I resulting in only partial enzymatic activity.

CLINICAL MANIFESTATIONS.

When this disorder presents in the neonatal period, unconjugated hyperbilirubinemia usually occurs during the first 3 days of life; serum bilirubin concentrations may be in a range compatible with physiologic jaundice or

may be at pathologic levels. The concentrations characteristically remain elevated into and after the 3rd wk of life, persisting in a range of 1.5-22 mg/dL; concentrations in the lower part of this range may create uncertainty about whether chronic hyperbilirubinemia is present. The onset of kernicterus is unusual. Stool color is normal, and the infants are without clinical signs or symptoms of disease. There is no evidence of hemolysis.

DIAGNOSIS.

Concentration of bilirubin in bile is nearly normal in type II syndrome. Jaundiced infants and young children having type II syndrome respond readily to 5 mg/kg/24 hr of oral phenobarbital with a decrease in serum bilirubin concentration to 2-3 mg/dL within 7-10 days. Those with type I syndrome do not respond.

TREATMENT.

Long-term reduction in serum bilirubin levels can be achieved with continued administration of phenobarbital at 5 mg/kg/24 hr. The cosmetic and psychosocial benefit should be weighed against the risks of an effective dose of the drug because there is a small long-term risk of kernicterus in the absence of hemolytic disease.

INHERITED CONJUGATED HYPERBILIRUBINEMIA

In inherited conjugated hyperbilirubinemias (see also Chapter 337), which are autosomal recessive disorders characterized by mild jaundice, the transfer of bilirubin and other organic anions from liver to bile is defective. Chronic mild conjugated hyperbilirubinemia is usually detected during adolescence or early adulthood but may occur as early as the 2nd year of life. The results of routine liver function tests are normal. Jaundice may be exacerbated with infection, pregnancy, oral contraceptives, alcohol consumption, or surgery. There is usually no morbidity, and life expectancy is normal; but these disorders may initially present difficult problems in the differential diagnosis of more serious diseases.

Dubin-Johnson Syndrome.

Dubin-Johnson syndrome is considered to be an autosomal recessive inherited defect in hepatocyte secretion of bilirubin glucuronide. The defect in hepatic excretory function is not limited to conjugated bilirubin excretion but also involves several organic anions normally excreted from the liver cell into bile. Absent function of multiple drug-resistant protein (MRP2), an adenosine triphosphate (ATP)-dependent canalicular transporter, is the responsible defect. Bile acid excretion is normal, and serum bile acid levels are normal. Urinary coproporphyrin excretion is normal in quantity; however, due to a defect in porphyrin excretion, coproporphyrin I constitutes 80% of the total. Coproporphyrin III is normally greater than 75% of the total. Cholangiography fails to visualize the biliary tract and roentgenography of the gallbladder is also abnormal. The liver cells contain black pigment similar to melanin.

Rotor Syndrome.

These patients have an additional deficiency in organic anion uptake. Total urinary coproporphyrin excretion is elevated, with a relative increase in the amount of the coproporphyrin I isomer. The gallbladder is normal by roentgenography, and liver cells contain no black pigment. Sulfobromophthalein excretion is often abnormal.

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